Claims

1. A substantially pure ribonucleic acid (RNA) complex comprising a first strand and a second strand that hybridize to each other under physiological conditions to form a double-strand region, said double-strand region comprising one or more mismatched regions that separate said double-strand region into two or more double-stranded segments, and

wherein said mismatched regions are capable of cleavage by single-strand ribonucleases.

2. A substantially pure ribonucleic acid (RNA) molecule comprising in 5' to 3' order, a first strand, a loop, and a second strand, wherein said first and second strands hybridize to each other under physiological conditions and said loop connects said first strand to said second strand to form at least one RNA double-stranded region, said RNA molecule further comprising one or more mismatched regions that separate the RNA double-stranded region into two or more double-stranded segments, and

wherein said mismatched regions are capable of cleavage by single-strand ribonucleases.

3. An RNA molecule having in 5' to 3' order a first strand and a second strand wherein said first and second strands hybridize to each other under physiological conditions to form a first double-stranded region and wherein said first and second strands are joined by a loop, wherein said RNA molecule further comprises a third strand and a fourth strand wherein said third and fourth strands hybridize to each other

under physiological conditions to form a second double-stranded region and wherein said second and third strands are joined by a fifth strand.

4. An RNA complex or RNA molecule of claims 1, 2, or 3, wherein at least one 5' end of an RNA molecule further comprises a Bernie Moss hairpin, said hairpin comprising in 5' to 3' order, an A strand and a B strand, said A strand and B strand capable of hybridizing under physiological conditions and said A strand and B strand joined by a loop, said B strand joined to the 5' end of said RNA molecule by a C strand, and wherein said Bernie Moss hairpin stabilizes said RNA complex or RNA molecule, relative to an RNA complex or RNA molecule lacking said Bernie Moss hairpin.

5. The RNA complex or RNA molecule of claim 1, 2, or 3 wherein at least a portion of at least one of said double-stranded segments has substantial sequence identity to a target polynucleotide, and wherein said ribonucleic acid molecule is capable of reducing expression of said target polynucleotide, relative to expression of said target polynucleotide in the absence of said ribonucleic acid molecule.

6. The RNA complex or RNA molecule of claim 1, 2, or 3 wherein at least one double-strand region comprises at least two mismatched regions that separate said double-stranded region into at least three double-stranded segments.

7. The RNA molecule of claim 5, wherein at least a portion of at least two of

said double-stranded segments has substantial sequence identity to a target polynucleotide.

8. The RNA molecule of claim 5, wherein one or more of said double-stranded regions has at least 18 contiguous nucleotides with substantial sequence identity to a target polynucleotide.

9. The RNA molecule of claim 8, wherein one or more of said double-stranded regions has at least 19 contiguous nucleotides with substantial sequence identity to a target polynucleotide.

10. The RNA molecule of claim 9, wherein one or more of said double-stranded regions has about 19 to 27 contiguous nucleotides with substantial sequence identity to a target polynucleotide.

11. The RNA molecule of claim 10, wherein one or more of said double-stranded regions comprises 19 to 30 contiguous nucleotides with substantial sequence identity to a target gene.

12. The RNA molecule of claim 3, wherein at least one of said double-stranded regions comprises a mismatched region.

13. The RNA molecule of claim 3, wherein both of said double-stranded

regions comprise a mismatched region.

14. The RNA molecule of claim 3, wherein at least one strand of at least one double-stranded region comprises a mismatched base pair.

15. The RNA molecule of claim 3, wherein said first and second strands each comprise at least one mismatched ribonucleic acid base.

16. The RNA molecule of claim 3, wherein a mismatched region of said second strand corresponds to the same position relative to a mismatched region of said first strand.

17. The RNA molecule of claim 3, wherein said mismatched region of said second strand corresponds to a different position relative to the mismatched region of said first strand.

18. The RNA complex or RNA molecule of claim 1, 2, or 3, wherein an RNA polynucleotide comprising the first or second strand comprises a 5' end single-strand overhang comprising at least one nucleotide, wherein said nucleotide does not base-pair with another nucleotide.

19. The RNA complex or RNA molecule of claim 1, 2, or 3, wherein the 3' end of an RNA polynucleotide comprising the first or second strands comprises a

single-strand overhang comprising at least one nucleotide, wherein said nucleotide does not base-pair with another nucleotide.

20. The RNA complex of claim 1, wherein both 5' ends have single-strand overhangs, wherein at least one nucleotide of said overhang does not base-pair with a nucleotide of said first strand.

21. The RNA complex of claim 1, wherein the 3' ends of the RNA polynucleotide comprising the first and second strands comprises a 3' single strand overhang, wherein at least one nucleotide of said overhang does not base-pair with another nucleotide.

22. The RNA molecule of claim 2 or 3, wherein said loop comprises 1 to 3 nucleotides that do not base-pair with a nucleotide of said RNA molecule.

23. The RNA molecule of claim 2 or 3, wherein said loop comprises 4 to 10 nucleotides that do not base-pair with a nucleotide of said RNA molecule.

24. The RNA molecule of claim 2 or 3, wherein said loop comprises 11 to 100 nucleotides that do not base-pair with a nucleotide of said RNA molecule.

25. The RNA molecule of claim 2 or 3 further comprising a mismatched region at the 5' end of a strand or the 3' end of a strand, wherein said mismatched

region comprises at least one nucleotide that does not base-pair with a nucleotide of said RNA molecule.

26. The RNA molecule of claim 3, wherein said double-strand region comprises at least one mismatched region.

27. The RNA molecule of claim 25, wherein said mismatched region comprises 1 nucleotide.

28. The RNA molecule of claim 25, wherein said mismatched region comprises about 2 to 7 nucleotides.

29. The RNA molecule of claim 25, wherein said mismatched region comprises about 10 to about 50 nucleotides.

30. The RNA molecule of claim 25, wherein said RNA molecule comprises a mismatched region at the 5' end of a strand that covalently links said RNA molecule to a 3' end of a strand of a second RNA molecule.

31. The RNA molecule of claim 25, wherein said RNA molecule comprises a mismatched region at the 3' end of a strand that covalently links said RNA molecule to a 5' end of a strand of a second RNA molecule or RNA complex of claims 1, 2, or 3.

32. The RNA molecule of claim 25, wherein said RNA molecule comprises at least one mismatched region that covalently links at least two RNA molecules of claims 2 or 3 in a 5' to 3' orientation to form a plurality of double-stranded regions comprising single stranded loops.

33. The RNA complex or RNA molecule of claims 1, 2, or 3 wherein at least three double-stranded segments are covalently linked by mismatched regions to form an RNA polynucleotide having at least three double-stranded regions, at least three loops and at least two mismatched regions.

34. The RNA molecule of claim 32, wherein at least one strand of said double-stranded regions has a sequence which is different and not complementary to at least one other strand.

35. The RNA complex or RNA molecule of claim 5, wherein said target gene is selected from the group consisting of a gene within the genome of the cell in which the RNA complex or RNA molecule is expressed (host gene), a gene of a pathogen, or a reporter gene.

36. The RNA molecule of claim 5, wherein at least a portion of one or more of said strands of one or more double-stranded regions has substantial sequence identity to a target gene selected from the group consisting of a host gene, a gene of a pathogen, or a reporter gene.

37. The RNA molecule of claim 35 or 36, wherein said host gene encodes a polypeptide associated with a biological activity of a cell.

38. The RNA molecule of claim 37, wherein said polypeptide is associated with a cancer, abnormal cell growth, a disease or disorder, or double-stranded ribonucleic acid (dsRNA)-mediated toxicity.

39. The RNA molecule of claim 38, wherein said disease or disorder is an autosomal dominant or recessive disorder.

40. The RNA molecule of claim 36, wherein said gene of a pathogen encodes a polypeptide associated with a biological activity of a pathogen.

41. The RNA molecule of claim 40, wherein said polypeptide is associated with infection, propagation, or pathogenesis of said pathogen in a host animal.

42. The RNA molecule of claim 41, wherein said polypeptide is a cellular receptor that mediates infection of a cell of said host animal by said pathogen

43. The RNA molecule of claim 40, wherein said pathogen is selected from the group consisting of a virus, a bacterium, a yeast, a protozoan, a fungus, and a parasite.

44. The RNA molecule of claim 37, wherein said cell is in a host animal.

45. The RNA molecule of claim 41 or 44, wherein said host animal is a mammal.

46. The RNA molecule of claim 45, wherein said mammal is a human.

47. A deoxyribonucleic acid (DNA) molecule comprising a region encoding an RNA molecule or RNA polynucleotide of an RNA complex of any one of claims 1-46.

45. 48. An expression construct comprising a sequence encoding at least one strand of an RNA complex of claim 1, or an RNA molecule of claims 2 or 3.

49. The expression construct of claim 48 which is a plasmid.

50. An expression construct comprising a first sequence encoding the first strand and a second sequence encoding the second strand of the RNA complex of claim 1.

51. A composition comprising at least two expression constructs, a first expression construct comprising a sequence encoding the first strand of the RNA

complex of claim 1 and a second expression construct comprising a sequence encoding the second strand of the RNA complex of claim 1.

52. A vector that comprises at least one DNA molecule of any one of claims 47-51.

53. The vector of claim 52, further comprising one or more of the following: a promoter, a 5' initiation sequence, a 3' termination sequence, a sequence encoding a 5' BM hairpin, a sequence encoding a constitutive transport element (CTE) sequence, a sequence encoding an intron sequence, an origin of replication, a sequence encoding a polyadenylation sequence, a sequence encoding a polymerase, or a sequence encoding a selectable marker.

54. The vector of claim 53, wherein said promoter is selected from the group consisting of an RNA Pol I promoter, an RNA Pol II promoter, an RNA Pol III promoter, and a mitochondrial promoter.

55. The vector of claim 54, comprising at least two promoters.

56. The vector of claim 53 comprising one or more promoters selected from the group consisting of: the HCMV promoter, the T7 promoter, the Sp6 promoter, the U6 promoter, the RSV promoter, a human mitochondrial light chain promoter, and a human mitochondrial heavy chain promoter.

57. The vector of claim 53, wherein said vector further encodes an RNA polymerase.

58. The vector of claim 57, wherein said polymerase is selected from a T7 RNA polymerase, an SP6 RNA polymerase, and a ribonucleic acid (RNA)-dependent RNA polymerase.

59. The vector of claim 53, wherein said selectable marker is hygromycin.

60. The vector of claim 53, wherein said intron comprises a sequence encoding an antibiotic resistance gene.

61. The vector of claim 59, wherein said antibiotic resistance gene is a eukaryotic antibiotic resistance gene or a prokaryotic antibiotic resistance gene.

62. The vector of claim 61, wherein said prokaryotic antibiotic resistance gene encodes an aminoglycoside.

63. The vector of claim 61, wherein said aminoglycoside is zeomycin, kanamycin, tobramycin, amikacin, spectinomycin, paromomycin, ribostamycin, butirosin, gentamycinB, lividomycin, or isepamicin.

64. The vector of claim 52, wherein said vector further comprises a nucleotide sequence encoding Dicer or Argonaut enzyme.

65. The vector of claim 52, wherein said DNA molecule of claim 47 comprises a first nucleic acid sequence that encodes said first strand of said RNA complex of claim 1 and a second nucleic acid sequence that encodes said second strand of said RNA complex of claim 1, wherein said first and said second nucleic acid sequences are expressed under the control of at least one promoter.

66. The vector of claim 65, wherein said first and said second nucleic acid sequences are under the control of the same promoter.

67. The vector of claim 65, wherein said first and said second nucleic acid sequences are under the control of different promoters.

68. The vector of claim 65, wherein said DNA molecule of claim 47 further comprises about 1 to 150 nucleotides that flank the 5' or 3' end of said region encoding said RNA molecule of any one of claims 1-46.

69. The vector of claim 68, wherein at least one of the nucleotides that flank said region is a purine and said purine is the 5' nucleotide of the polynucleotide sequence.

70. The vector of claim 69, wherein said 5'-most 1 to 4 nucleotides are guanosines.

71. A pharmaceutical composition comprising the ribonucleic acid molecule of any one of claims 1-46 and a physiologically acceptable excipient.

72. A pharmaceutical composition comprising the deoxyribonucleic acid molecule of claim 47 and a physiologically acceptable excipient.

73. A pharmaceutical composition comprising the vector or construct of any one of claims 48-70 and a physiologically acceptable excipient.

74. A method for generating the ribonucleic acid (RNA) molecule of any one of claims 1-46, said method comprising contacting a deoxyribonucleic acid (DNA) molecule of claim 47 or the vector or construct of any one of claims 48-70 with cell-free components, or administering the DNA molecule of claim 47 or the vector or construct of any one of claims 48-70 to a cell or a mammal, under conditions that allow transcription of said DNA molecule to produce said RNA molecule.

75. A method for reducing or inhibiting expression of a gene by a cell, said method comprising administering a ribonucleic acid (RNA) molecule of any one of claims 1-46 to said cell, or administering a deoxyribonucleic acid (DNA) molecule of claim 47 or a vector or construct of any one of claims 48-70 to said cell under

conditions that allow transcription of said first DNA molecule to form RNA molecule, wherein at least a portion of one or more double-stranded regions of said RNA molecule have substantial sequence identity to all or a portion of a first target gene or an RNA molecule transcribed from said first target gene, and wherein following cleavage of said first RNA molecule by a single-stranded RNA-specific RNase to liberate double-stranded regions of said RNA molecule, said liberated double-stranded regions from said RNA molecule having substantial sequence identity to all or a portion of said target gene and capable of reducing expression of said target gene by said cell, relative to expression of said target gene by a cell not administered said RNA molecule, said DNA molecule, or vector.

76. The method of claim 74, wherein said cell is a mammalian cell or a cell of a pathogen.

77. The method of claim 75, wherein said mammalian cell or said cell of a pathogen is in a mammal.

78. The method of claim 77, wherein said mammal is a human.

79. The method of claim 77, wherein said cell of a pathogen is a bacterial cell, a yeast cell, a protozoan cell, a fungal cell, or a cell of a parasite.

80. The method of claim 77, wherein said mammalian cell is infected with a

virus and said target gene is a viral gene or an RNA transcribed from said viral gene, wherein said method comprises reducing expression of said viral gene, relative to the expression of a viral gene in a mammalian cell infected with said virus but not administered said RNA molecule, said DNA molecule, or said vector.

81. The method of claim 75, wherein at least a portion of one or more of said double-stranded regions of said RNA molecule have substantial sequence identity to all or a portion of a second target gene, or an RNA molecule transcribed from said second target gene, wherein said second target gene encodes a polypeptide associated with an interferon response or dsRNA-mediated toxicity, and wherein said liberated double-stranded regions of said first RNA molecule with substantial sequence identity to all or a portion of said second target gene reduce said interferon response or dsRNA-mediated toxicity in said cell, relative to a cell not administered said first RNA molecule, said first DNA molecule, or said first vector.

82. The method of claim 75, wherein said method further comprises administering a second RNA molecule of any one of claims 1-46 to said cell, or administering a second DNA molecule of claim 47 or a second vector or construct of any one of claims 48-70 comprising said second DNA molecule of claim 47 to said cell under conditions that allow transcription of said second DNA molecule to form said second RNA molecule, wherein one or more double-stranded regions of said second RNA molecule have substantial sequence identity to a target gene, or a ribonucleic acid molecule transcribed from said target gene, wherein said target gene

encodes a polypeptide associated with an interferon response or dsRNA-mediated toxicity, and wherein following cleavage of said second RNA molecule by a single-stranded RNA-specific RNase to produce liberated double-stranded regions of said second RNA molecule, wherein said liberated double-stranded regions of said second RNA molecule with substantial sequence identity to said target gene reduce said interferon response or dsRNA-mediated toxicity in said cell, relative to a cell not administered said second RNA molecule, said second DNA molecule, or said second vector.

83. A method for treating or preventing a disease or disorder in a mammal, said method comprising administering a first ribonucleic acid (RNA) molecule of any one of claims 1-46 to said mammal, or administering a first deoxyribonucleic acid (DNA) molecule of claim 47 or a first vector or construct of any one of claims 48-70 comprising said first DNA molecule of claim 47 to a cell of said mammal under conditions that allow transcription of said first DNA molecule to form said first RNA molecule, wherein at least a portion of one or more double-stranded regions of said first RNA molecule have substantial sequence identity to all or a portion of a first target gene, or an RNA molecule transcribed from said first target gene, wherein said first target gene encodes a polypeptide associated with said disease or disorder, and wherein following cleavage of said first RNA molecule by a single-stranded RNA-specific RNase to produce liberated double-stranded regions of said first RNA molecule, wherein said liberated double-stranded regions of said first RNA molecule with substantial sequence identity to said first target gene reduce expression of said

first target gene by said mammal, relative to expression of said first target gene by a mammal not administered said first RNA molecule, said first DNA molecule, or said first vector, and wherein said reduction of expression of said first target gene treats or prevents said disease or disorder.

84. The method of claim 83, wherein said disease or disorder is cancer, systemic lupus erthyematosis, Alzheimer's disease, or Huntington's disease.

85. The method of claim 84, wherein said cancer is selected from the group consisting of prostate cancer, breast cancer, ovarian cancer, pancreatic cancer, gastric cancer, bladder cancer, salivary gland carcinoma, gastrointestinal cancer, lung cancer, colon cancer, melanoma, brain tumor, leukemia, lymphoma, and carcinoma.

86. The method of claim 83, wherein at least a portion of one or more of said double-stranded regions of said first RNA molecule have substantial sequence identity to all or a portion of a second target gene, or an RNA molecule transcribed from said second target gene, wherein said second target gene encodes a polypeptide associated with an interferon response or dsRNA-mediated toxicity, and wherein following cleavage of said first RNA molecule by a single-stranded RNA-specific RNase to produce liberated double-stranded regions of said first RNA molecule, wherein said liberated double-stranded regions from said first RNA molecule with substantial sequence identity to said second target gene reduces said interferon response or dsRNA-mediated toxicity in said mammal, relative to a mammal not administered

said first RNA molecule, said first DNA molecule, or said first vector.

87. The method of claim 83, wherein said method further comprising administering a second RNA molecule of any one of claims 1-46 to said mammal, or administering a second DNA molecule of claim 47 or a second vector or construct of any one of claims 48-70 comprising said second DNA molecule of claim 46 to a cell of said mammal under conditions that allow transcription of said second DNA molecule to form said second RNA molecule, wherein at least a portion of one or more double-stranded regions of said second RNA molecule have substantial sequence identity to a target gene, or an RNA molecule transcribed from said target gene, wherein said target encodes a polypeptide associated with an interferon response or dsRNA-mediated toxicity, and wherein following cleavage of said second RNA molecule by a single-stranded RNA-specific RNase to produce liberated double-stranded regions of said second RNA molecule, wherein said liberated double-stranded regions from said second RNA molecule with substantial sequence identity to said target gene reduces said interferon response or dsRNA-mediated toxicity in said mammal, relative to a mammal not administered said second RNA molecule, said second DNA molecule, or said second vector.

88. A method for treating or preventing infection of a mammal by a pathogen, said method comprising administering a first ribonucleic acid (RNA) molecule of any one of claims 1-46 to said mammal, or administering a first DNA molecule of claim 47 or a first vector or construct of any one of claims 48-70 comprising said first DNA

molecule of claim 47 to a cell of said mammal under conditions that allow transcription of said DNA molecule to form said RNA molecule, wherein at least a portion of one or more double-stranded regions of said first RNA molecule have substantial sequence identity to all or a portion of a first target gene, or an RNA molecule transcribed from said first target gene, wherein said first target gene encodes a polypeptide associated with a biological activity of said pathogen, and wherein following cleavage of said first RNA molecule by a single-stranded RNA-specific RNase to produce liberated double-stranded regions of said first RNA molecule, wherein said liberated double-stranded regions from said first RNA molecule with substantial sequence identity to said first target gene reduces expression of said first target gene in said pathogen or in a cell of said mammal infected with said pathogen, relative to expression of said first target gene in a pathogen, or in a cell of a mammal infected with said pathogen, not exposed to said first RNA molecule, said first DNA molecule, or said first vector, and wherein said reduction of expression of said first target gene treats or prevents said infection.

89. The method of claim 88, wherein said pathogen is selected from the group consisting of a virus, a bacterium, a yeast, a fungus, a protozoan, and a parasite.

90. The method of claim 88, wherein said biological activity is associated with infection, propagation, or pathogenesis of said pathogen in said mammal.

91. The method of claim 88, wherein said first target gene encodes a cellular

receptor that mediates infection of a cell of said mammal by said pathogen.

92. The method of claim 88, wherein said mammal is a human.

93. The method of claim 88, wherein said infection is caused by the implantation of a device in said mammal.

94. The method of claim 93, wherein said method further comprises contacting said device with said first RNA molecule prior to, concurrent with, or following administration of said device to said mammal.

95. The method of claim 93, wherein said device is a surgical implant, a prosthetic device, or a catheter.

96. The method of claim 88, wherein at least a portion of one or more of said double-stranded regions of said first RNA molecule have substantial sequence identity to all or a portion of a second target gene, or an RNA molecule transcribed from said second target gene, wherein said second target gene encodes a polypeptide associated with an interferon response or dsRNA-mediated toxicity, and wherein following cleavage of said first RNA molecule by a single-stranded RNA-specific RNase to produce liberated double-stranded regions of said first RNA molecule, wherein said liberated double-stranded regions from said first RNA molecule with substantial sequence identity to said second target gene reduces said interferon response or

dsRNA-mediated toxicity in said mammal, relative to a mammal not administered said first RNA molecule, said first DNA molecule, or said first vector.

97. The method of claim 88, wherein said method further comprises administering a second RNA molecule of any one of claims 1-46 to said mammal, or administering a second DNA molecule of claim 47 or a second vector or construct of any one of claims 48-70 comprising said second DNA molecule of claim 47 to said mammal under conditions that allow transcription of said second DNA molecule to form said second RNA molecule, wherein at least a portion of one or more double-stranded regions of said second RNA molecule have substantial sequence identity to a target gene, or a ribonucleic acid molecule transcribed from said target gene, and wherein said target gene encodes a polypeptide associated with an interferon response or dsRNA-mediated toxicity, and wherein following cleavage of said second RNA molecule by a single-stranded RNA-specific RNase to produce liberated double-stranded regions of said second RNA molecule, wherein said liberated double-stranded regions from said second RNA molecule with substantial sequence identity to said target gene reduces said interferon response or dsRNA-mediated toxicity in said mammal, relative to a mammal not administered said second RNA molecule, said second DNA molecule, or said second vector.

98. A method for treating or preventing an immune response by a mammal to a transplanted cell, tissue, or organ, said method comprising administering a first ribonucleic acid (RNA) molecule of any one of claims 1-46 to said mammal prior to,

concurrent with, or following transplantation of said cell, tissue or organ, or administering a first deoxyribonucleic acid (DNA) molecule of claim 47 or a first vector or construct of any one of claims 48-70 comprising said first DNA molecule of claim 47 to said mammal prior to, concurrent with, or following transplantation of said cell, tissue or organ under conditions that allow transcription of said first DNA molecule to form said RNA molecule, wherein at least a portion of one or more double-stranded regions of said first RNA molecule have substantial sequence identity to all or a portion of a first target gene, or an RNA molecule transcribed from said first target gene, and wherein said first target gene is associated with an immune response to said transplanted cell, tissue, or organ, and wherein following cleavage of said first RNA molecule by a single-stranded RNA-specific RNase to produce liberated double-stranded regions of said first RNA molecule, wherein said liberated double-stranded regions from said first RNA molecule with substantial sequence identity to said first target gene reduces expression of said first target gene in said mammal, relative to expression of said first target gene in a mammal not administered said first RNA molecule, said first DNA molecule, or said first vector, and wherein said reduction of expression of said gene treats or prevents said immune response.

99. The method of claim 98, wherein at least a portion of one or more of said double-stranded regions of said first RNA molecule have substantial sequence identity to a second target gene, or an RNA molecule transcribed from said second target gene, wherein said target gene encodes a polypeptide associated with an interferon response or dsRNA-mediated toxicity, and wherein following cleavage of said first RNA

molecule by a single-stranded RNA-specific RNase to produce liberated double-stranded regions of said first RNA molecule, wherein said liberated double-stranded regions from said first RNA molecule with substantial sequence identity to said second target gene reduces said interferon response or dsRNA-mediated toxicity in said mammal, relative to a mammal not administered said first RNA molecule, said first DNA molecule, or said first vector.

100. The method of claim 98, wherein said method further comprising administering a second RNA molecule of any one of claims 1-46, or administering a second DNA molecule of claim 47 or a second vector or construct of any one of claims 48-70 comprising said second DNA molecule of claim 47 to said mammal under conditions that allow transcription of said second DNA molecule to form said second RNA molecule, wherein at least a portion of one or more double-stranded regions of said second RNA molecule have substantial sequence identity to a target gene, or an RNA moleule transcribed from said target gene, wherein said target gene encodes a polypeptide associated with an interferon response or dsRNA-mediated toxicity, and wherein following cleavage of said second RNA molecule by a single-stranded RNA-specific RNase to produce liberated double-stranded regions of said second RNA molecule, wherein said liberated double-stranded regions from said second RNA molecule with substantial sequence identity to said target gene reduces said interferon response or dsRNA-mediated toxicity in said mammal, relative to a mammal not administered said second RNA molecule, said second DNA molecule, or said second vector.

101. The method of any one of claims 75, 83, 88, or 98, wherein expression of said first target gene is reduced by at least 20%.

102. The method of any one of claims 75, 83, 88, or 98, wherein expression of said first target gene is reduced by at least 60%.

103. The method of any one of claims 75, 83, 88, or 98, wherein expression of said first target gene is reduced by at least 95%.

104. The method of any one of claims 81, 82, 86, 87, 96, 97, 99, or 100, wherein said interferon response or dsRNA-mediated toxicity is reduced by at least 20%.

105. The method of any one of claims 81, 82, 86, 87, 96, 97, 99, or 100, wherein said interferon response or dsRNA-mediated toxicity is reduced or inhibited by at least 60%.

106. The method of any one of claims 81, 82, 86, 87, 96, 97, 99, or 100, wherein said interferon response or dsRNA-mediated toxicity is reduced or inhibited by at least 95%.

107. The method of any one of claims 83, 88, or 98, wherein said mammal is a human.

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